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AN UNBIASED MONTHLY COVERING ALL THINGS PSYCHIATRIC

Steve Balt, MD
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IN THIS ISSUE

Focus of the Month:
Pharmacogenetics

Learning objectives for this issue:
1. Determine some of the pharmacogenetic tests that can possibly play a role in clinical psychiatry. **2.** Describe the uses of pharmacogenetic testing and reasons why a psychiatrist would consider genetic testing on patients. **3.** Explain what is known about the new insomnia drug suvorexant (Belsomra), which was approved by the FDA. **4.** Summarize some of the current findings in the literature regarding psychiatric treatment.

Pharmacogenetic Testing in Clinical Psychiatry

Robert H. Howland, MD
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Dr. Howland has disclosed that he has no relevant financial or other interests in any commerical companies pertaining to this educational activity.

"Personalized medicine" is a buzzword in healthcare and stems from the idea that treatments can be designed specifically for a patient, based on his or her own biological characteristics.

In psychiatry, personalization is largely based on "pharmacogenetics," the selection of medications based on genetic factors associated with drug response and tolerability. Could your patient's genetic code predict which medications you prescribe?

It's important to point out that some genes affect *pharmacokinetics*

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In Summary

- The pharmacogenetic testing industry is severely underregulated—companies don't have to prove their tests are valid before marketing them
- The most comprehensive literature review found no compelling evidence that these tests affect clinical outcome
- The tests are expensive and should be ordered sparingly, if at all

Q& With A the Expert

The Uses of Pharmacogenetic Testing

Steven Hamilton, MD, PhD

Psychiatrist, The Permanente Medical Group
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Clinical faculty, Department of Psychiatry
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Dr. Hamilton has disclosed that he is an unpaid scientific advisor to 23andMe, which offers a commercial genome test. Dr. Balt has reviewed this interview and found no evidence of bias in this educational activity.

TCPR: Dr. Hamilton, why would a psychiatrist want or need to order genetic testing on a patient?

Dr. Hamilton: I tend to consider genetic testing for two specific types of cases. One is serial intolerability—poor tolerance of multiple medications, for instance, across SSRIs or even between classes of medications. This gets me wondering if a person has some perturbation in their metabolism; a genetic variant that might affect how they process these drugs. The other indication is when a patient shows resistance to antipsychotics or to antidepressants.

TCPR: Can you summarize briefly some of the genes that are tested in pharmacogenetic testing in psychiatry?

Dr. Hamilton: Because of their connection to a broad swath of psychotropic drugs, it really boils down to two cytochrome P450 genes: 2D6 and 2C19. This is because nearly all psychotropics are metabolized to some extent by the enzymes encoded by these genes. More importantly, there is ample genetic variation in these genes, specifically related to people being poor metabolizers, and these are fairly common in the general

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while others involve *pharmacodynamic* processes. Pharmacokinetics refers to how quickly and efficiently a drug reaches its target and how quickly it leaves the body: drug absorption, distribution, metabolism, and excretion. Clinically, the most important contributor is the cytochrome P-450 (CYP450) system, which accounts for the metabolism of approximately 60% of prescribed drugs.

Multiple CYP450 enzymes exist and are classified according to a standardized nomenclature. The major enzymes of interest in clinical psychopharmacology are 1A2, 2B6, 2C9, 2C19, 2D6, and 3A4. For instance, fluoxetine is a substrate of 2D6; increased activity of this enzyme means lower blood levels of fluoxetine, while decreased activity corresponds to higher blood levels.

Pharmacodynamics, on the other hand, refers to the mechanism of action of a drug at its particular target(s). Whenever you prescribe a psychotropic drug, you are (most likely) thinking about the drug's targets: receptors, transporters, or enzymes. Each of these directly or indirectly regulates the synthesis, transmission, or degradation of neurotransmitters such as serotonin and dopamine. Similar to the enzymes mentioned above, pharmacodynamic targets exist as proteins produced by different genes. Slight variations in the coding for a particular gene are referred to as *polymorphisms*, and these can alter the amount, structure, binding, or function of these proteins. In turn, these differences in the protein targets can influence the therapeutic or adverse effects of the drugs you prescribe.

For a well-known example of pharmacodynamic variation, consider the serotonin reuptake transporter (SERT). SERT regulates the reuptake of serotonin into neurons, and is the main site of action of selective serotonin reuptake inhibitor (SSRI) antidepressant drugs. Multiple genetic polymorphisms in SERT have been identified. Some research suggests that patients carrying certain SERT polymorphisms (such as the S or "short" allele) may respond less well to SSRI drugs and may experience more adverse effects of SSRIs, but the correlation is not absolute.

Polymorphisms of other genes involved in the pharmacodynamics of drug response, such as serotonin (5-HT) receptors, dopamine receptors, and other transporters, have been studied. But no single genetic difference, as of now, is significant enough to predict an outcome when you prescribe a drug.

Pharmacogenetic Tools

In recent years, numerous products have come on the market to analyze genetic polymorphisms. The first commercially available product was the AmpliChip CYP450 Test, developed by Roche Diagnostics and approved by the FDA in 2004. Using a small blood sample from the patient, it analyzes genetic polymorphisms associated with two metabolizing enzymes (2D6 and 2C19). Based on the patient's 2D6 and 2C19 polymorphisms, his or her 2D6 metabolic activity is characterized as poor, intermediate, extensive, or ultra-rapid, and 2C19 activity as poor or extensive. This information can theoretically be used to make clinical decisions about drugs that are 2D6 or 2C19 substrates.

Many newer pharmacogenetic tests, based on similar technology, are currently available on the market. The most popular ones include Genecept and GeneSight. These tests analyze the majority of the known 450 enzyme polymorphisms, as well as various combinations of pharmacodynamic genes.

Laboratory Tests are Under-regulated by FDA

Despite their ready availability, does pharmacogenetic testing make sense for your patient? Does it really matter whether the patient in front of you is a "fast" or a "slow" metabolizer of a drug you are prescribing?

The answer to these key questions comes down to data, which I'll review later in this article. But first, it's important to know a bit about how these tests are regulated (or, more accurately, under-regulated). We are all familiar with the standards used by the FDA to approve medications: companies must submit double-blind, placebo-controlled trials and the FDA carefully scrutinizes the data before finally rendering a decision about approval.

Not so with laboratory tests. In fact, there are no specific federal requirements for laboratories to establish or verify the clinical validity of their tests, and laboratories generally do not have the capability to develop evidence of clinical utility. The bottom line is that the availability of a test should not be assumed to be proof that it has been proven to enhance clinical outcomes. Partly because of this problem, the FDA is currently developing draft guidelines on the regulation of laboratory tests, which would include pharmacogenetic test products.

What Does The Data Show?

Seven years ago, the federal Agency for Healthcare Research and Quality (AHRQ) reviewed existing studies to determine if testing for 450 polymorphisms in patients taking SSRIs leads to improvement in outcomes or

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if testing results are useful in medical, personal, or public health decision-making (Thakur M et al, *Genet Med* 2007;9(12):826–835). The review revealed few high-quality, clinical studies. Several studies included non-randomized design, small numbers of subjects, and a failure to account for other genetic factors that may influence SSRI response or tolerability. There were no prospective studies of P450 genotyping and its relationship to clinical outcomes. There was no correlation between P450 polymorphisms and SSRI drug levels, efficacy, or tolerability. There were no data regarding whether testing leads to improved depression outcomes; whether testing influences medical, personal, or public health decision-making; or whether any harms are associated with testing itself or with subsequent management decisions. A more recent study found no clear benefit of testing for pharmacodynamic targets (de Leon J, *Pharmacol Res* 2009;59(2):81–89).

All this negative data has not dissuaded testing companies from marketing their products to us, sometimes aggressively so. The "GeneSight Psychotropic" test, offered by Assurex Health, detects genetic polymorphisms associated with six metabolic enzymes (1A2, 2B6, 2C9, 2C19, 2D6, and 3A4) and two pharmacodynamic genes (5HT2A and SERT). They claim that the results are potentially relevant to the use of 22 antidepressant drugs and 16 antipsychotic drugs.

The testing process is quite simple: blood samples or mouth swabs are sent to a central laboratory for analysis, and the results (available in 36 hours) categorize each of these 38 drugs into one of three groups: 1) little or no gene-drug interaction; 2) moderate gene-drug interaction; and 3) severe gene-drug interaction. For a particular patient, the use of drugs within each group is characterized as "use as directed" (referred to as "green bin" drugs), "use with caution" ("yellow bin"), and "use with caution and with more frequent monitoring" ("red bin"). The "green bin" drugs require no special dosing considerations for the patient. For drugs within the yellow and red "bins," additional comments about their potential use are provided in the laboratory report. These comments might explain expected changes in drug blood levels (such as too high or too low) or expected clinical effects (such as reduced efficacy or increased side effects).

Does this information lead to better clinical outcomes? Two open-label studies have reported that GeneSight Psychotropic was effective for managing patients with depression (Hall-Flavin DK et al, *Transl Psychiatry* 2012;2:e172; Hall-Flavin DK et al, *Pharmacogenet Genomics* 2013;23(10):535–548). In each study, a pharmacogenetic testing report was used to guide the selection and dosing of medication for one patient cohort, but not for the other cohort. The guided group in each study had greater depression symptom improvements. However, there were methodological problems. Patients were not randomly assigned to the groups. Also, prescribers and patients in each group were not fully blinded—potentially leading to a placebo effect that could artificially improve the outcomes for those who got the testing. Moreover, although these studies were funded by Mayo Clinic research grants, most of the authors have significant financial relationships with Assurex Health, which could have further biased the outcomes.

The company subsequently funded a prospective double-blind randomized trial, comparing the use of GeneSight Psychotropic to treatment without these test results. There was a slightly greater improvement in depression scores with guided treatment, but the difference between groups was not statistically significant (Winner JG et al, *Discov Med* 2013;16(89):219–227). The overall likelihood of medication switches, augmentations, or dose-adjustments did not differ between groups. However, a subanalysis showed that GeneSight subjects taking a "red bin" medication at baseline were significantly more likely to have this medication changed and, afterward, had significantly improved depression scores than unguided subjects taking a "red bin" medication. Overall, not very impressive results.

Assurex Health has commercialized two other pharmacogenetics products: GeneSight ADHD (released in May 2012) and GeneSight Analgesic (released

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News of Note

Research Indicates Schizophrenia is Eight Distinct Disorders

If you thought schizophrenia was a single disorder, new research suggests that you may need to rethink this point of view.

According to researchers schizophrenia may be a group of eight distinct disorders, each caused by changes in clusters of genes that lead to different sets of symptoms. The finding may lead to the development of better ways to diagnose and treat schizophrenia, C. Robert Cloninger, a co-author of the study, told *USA Today* (http://usat.ly/1y5FMbH).

In the study, which was published in September (Arnedo J et al, *Am J Psychiatry* 2014, Epub ahead of print), researchers compared the DNA of 4,200 people with schizophrenia to that of 3,800 people without the disorder. They found schizophrenia is a group of heritable disorders caused by a moderate number of separate genotypic networks associated with several distinct clinical syndromes. Certain genetic profiles matched particular symptoms. For example, people with one genetic cluster have disorganized speech while those with another genetic profile hear voices. Some genetic clusters give people higher risks of the disorder as well, with one set conferring a 95% chance of developing schizophrenia, the study found.

Cloninger, professor of psychiatry and genetics at the Washington University School of Medicine in St. Louis, told the newspaper he hopes the work will open the door to treating the cause, rather than just the symptoms, of schizophrenia.

Expert Interview

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population. And with CYP2D6, there is an added level of complexity in that you can have individuals who are what we term *ultra*-metabolizers, meaning their gene products work at a much higher rate of efficiency than the normal level of functioning.

TCPR: You talk about people being normal metabolizers or poor metabolizers on these genes. What is the evidence that metabolizer status correlates with blood levels of medication and/or clinical outcome?

Dr. Hamilton: There has been a lot of effort put into looking at the correlation between drug levels and polymorphism status. The evidence is good in the case of tricyclic antidepressants. The classic study from the '90s showed that nortriptyline levels were highly correlated with metabolizer status for 2D6 (Dalén P et al, *Clin Pharmacol Ther* 1998;63(4):444–452). Those who were ultra-metabolizers had almost unmeasurable amounts of nortriptyline in their system. So there are a few clinical observations, such as this, but these are typically clinical pharmacokinetic laboratory studies. What's really missing are large prospective studies looking at actual clinical outcomes based on metabolizer status.

> **"There have never been any consistent correlations between clinical response to medications and any of these particular genotypes."**
>
> Steven Hamilton, MD, PhD

TCPR: Do you think it is possible that there is a sort of intuitive pharmacogenetics going on all the time in psychiatry? That patients who are regular or poor metabolizers end up on the appropriate dose of medication through the normal process of monitoring and titrating medication?

Dr. Hamilton: Some research shows that, yes, clinicians frequently alter the dose of an individual's medication in the direction that fits, using a sort of intuitive pharmacogenetics. An older study looked at the genotypes of people taking risperidone (Risperdal). Investigators looked at individuals' doses of risperidone over time, and later looked at their genotypes. You would expect that individuals who were poor metabolizers probably couldn't tolerate higher doses because it was cleared less efficiently. Sure enough, individuals who had poor-metabolizer status were placed on lower doses, even though the clinicians did not know anything about their P-450 enzymes (Mas S et al, 2012 *Pharmacogenomics J*;12(3):255–259).

TCPR: The massive STAR*D trial found no individual antidepressant strategy to be better than any other. Is it possible that applying pharmacogenetic strategies to patients in order to guide treatment might have led to better outcomes in a study like STAR*D?

Dr. Hamilton: My own work was involved with genetic studies of the STAR*D sample. We carried out a retrospective genome-wide association study (GWAS) of the STAR*D data. The results we found and published did not meet the standard levels of statistical significance, and were not robust enough to have warranted changing the treatment, even if we had that information before the STAR*D study began. There is an exception to that. We found that CYP2D6 or CYP2C19 metabolizer status did not predict response, and published that finding some time ago (Peters EJ et al, 2008 *PLoS One,* 3(4):e1872). However, in work that we did not publish then, we looked at 2D6 and 2C19 metabolizer status and found that the rates of intolerability—defined by STAR*D as whether an individual could continue taking the medication based on side effects—was correlated with 2D6 and 2C19 genotypes. Knowing that ahead of time may have been useful, because one of the primary predictors of antidepressant response in STAR*D was drug intolerability.

TCPR: Are there any guidelines for the use of pharmacogenetic testing to optimize drug therapy?

Dr. Hamilton: There are about 25 psychotropic drugs for which the FDA has guidance for pharmacogenetics (these can be found at http://1.usa.gov/1cCZvmr). It is an interesting list that I would urge clinicians to check out. Another resource is the Clinical Pharmacogenetics Implementation Consortium (CPIC), a partly NIH-funded group of researchers, in this field, who have come together to create guidelines (www.pharmgkb.org/page/cpic). They provide recommendations for a broad array of medications, including several tricyclic antidepressants.

TCPR: Isn't it true that behavioral factors contribute to drug response in a way that might outweigh the genetic factors?

Dr. Hamilton: Absolutely. Genetics only make up a small part of the likelihood of drug response or tolerability, and other issues are strong contributors. Other exogenous substances, such as tobacco or dietary supplements, may interfere with the metabolism of antidepressants and other metabolic issues related to age, disease (eg, hepatic disorders), and gender can influence these things. Genetics likely plays some discrete, but measurable, role, but it needs to be taken into account with all these other nongenetic factors.

TCPR: You mentioned the genome-wide association study (GWAS) analysis. What is GWAS?

Dr. Hamilton: GWAS allows us to look not at just a few genes, but tens of thousands of genes and millions of genetic polymorphisms simultaneously. GWAS asks whether variations from numerous genes across the genome, each of which might contribute only a small amount individually, might together influence a phenotype. Also, the question can be asked whether combinations of variants from a multitude of genes influence medication response. In a recent article, we combined all the data from large European and American studies and it was still insufficient to see anything of strong statistical significance. The individual contribution to antidepressant response by variation from numerous genes is of such low amplitude that we can't detect it with the numbers of samples that we have (GENDEP Investigators, MARS Investigators, STAR*D Investigators, *Am J Psychiatry* 2013;170(2):207–217). In the case of schizophrenia, a recent study suggested that there are over 100 variants that influence risk for this disorder. But it took tens of thousands of samples to find them. It is one thing to find someone with a particular disease phenotype, but to find someone who has gone through a clinical trial with a well-delineated treatment response phenotype—is much more difficult. So for

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Belsomra: A New Hypnotic? Don't Get Too Excited

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Dr. Puzantian has disclosed that she has no relevant relationships or financial interests in any commercial company pertaining to this educational activity.

In the wake (pun intended) of last year's FDA warnings of next-morning impairment and the lower dosing recommendations for "Z drugs," wouldn't now be the perfect time for a new hypnotic to enter the marketplace?

Suvorexant, which will be marketed by Merck & Co. under the brand name Belsomra, was approved by the FDA in August 2014. It truly is a new chemical entity with a first-in-kind mechanism of action. Unlike currently marketed hypnotics, suvorexant does not exert its hypnotic effects via activity at receptors for GABA, histamine, or melatonin. Considered a "DORA" or dual orexin (OX1 and OX2) receptor antagonist, suvorexant alters the signaling of orexins. Orexins are neurotransmitters that regulate the sleep-wake cycle by promoting wakefulness through excitement of brain regions involved in arousal and attention.

But what does this mean clinically? Does it work? Is it safe? What about long-term use?

What Studies Show

Several pre-clinical trials have examined the efficacy and safety of suvorexant in 1,784 patients with insomnia, with 160 patients taking the drug for one year or longer. Compared to patients taking placebo, those taking suvorexant tended to go to sleep more quickly (depending on the study and the dosage used, an average of about two to 22 minutes faster) and spent less time awake throughout the night (on average, about 20 minutes more total sleep time). In general, the higher doses (30 mg to 40 mg) tended to be more effective than the lower doses (15 mg to 20 mg). These studies all compared suvorexant with placebo, so unfortunately there is no data allowing us to compare it with the hypnotics currently in use.

The most common side effects were somnolence, headache, abnormal dreams, and dry mouth, which were reported in about 2% to 8% of patients in the studies. There were also some rare side effects (reported in less than 1% of patients) that could become quite problematic. These include sleep paralysis (inability to speak or move for up to a few minutes during the sleep-wake transition), cataplexy (leg weakness for seconds up to a few minutes, reported both in the nighttime and daytime), and hypnagogic hallucinations (including vivid and disturbing perceptions).

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Expert Interview

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our meta-analysis we only had several thousand individuals, which is probably insufficient to find the pattern of variation that would help in what you are describing for personalizing medication choice.

TCPR: Can you describe what pharmacogenetic tests are currently available to psychiatrists?

Dr. Hamilton: A great resource is a website called GeneTests.org. It is a compendium of genetic tests, not only for rare genetic disorders, but also more common tests as well. You can search for a genetic test and it will actually give you a list of all the different providers of this test. An alternative website, where practitioners can get information about genetic tests, their costs, and comparisons, is Nextgxdx.com. There are several commercial operations that sell tests for psychiatric applications. I am not recommending any of them, in any way, by mentioning them. They include Genomind, Pathway Genomics, Genelex, and Assurex Health.

TCPR: In addition to 2D6 and 2C19, there are other pharmacokinetic genes, as well as a number of pharmacodynamics genes, such as the serotonin transporter (SLC6A4), DRD2, and MTHFR, offered as a part of commercial tests. Do these also help to guide treatment options?

Dr. Hamilton: To put it simply, no. In my work studying all of these genes, as well as the work of many others, there have never been any consistent correlations between clinical response to medication and any of these particular genotypes. They are very appealing because they get at presumptive mechanisms for these drugs, but when you actually look at large samples for which there is statistical power to detect an association, the findings are either inconsistent or just don't exist. The evidence just does not support any of them at this time.

TCPR: These tests have a reputation for being expensive. How much do they cost?

Dr. Hamilton: The prices for a relatively focused gene panel such as 2D6 and 2C19, in general, run in the hundreds of dollars. I am not aware of a strong push to get insurance companies to pay for these.

TCPR: Can you speak to the applications of commercial genome tests such as the one offered by 23andMe? Could a commercial test such as that give me the same information as these pharmacogenetic tests?

Dr. Hamilton: 23andMe offers an inexpensive genome test—about $99. I think it gives data on about a million genetic variants, including functional variants in 2C19. The information provided depends on the variant. For instance, the 2D6 region is so extremely complicated at the structural level that many of these commercial genome-wide tests such as 23andMe do not really test that gene very well, if at all. On the other hand, the information about 2C19 is in there, along with several other variants. Right now, the FDA does not allow 23andMe to give you any advice relating to the variant.

TCPR: Are you aware of any pharmaceutical developments capitalizing on specific pharmacodynamic polymorphisms?

Dr. Hamilton: There are examples from the cancer literature where specific drugs are targeted to particular mutations in tumors, but we are not there yet for psychotropics.

TCPR: Thank you, Dr. Hamilton.

Research Updates IN PSYCHIATRY

Section Editor, Glen Spielmans, PhD

Glen Spielmans, PhD, has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

DEPRESSION

Physicians May Overprescribe Antidepressants Based on Brief Depression Questionnaires

Brief depression screening questionnaires are popular, especially with primary care providers (PCPs). However, a new study suggests that PCPs who use these questionnaires might be prescribing antidepressants to patients who don't need them.

This was a prospective study of patients at six primary care office locations in California. Each patient was administered the Patient Health Questionnaire-9 (PHQ-9) by the researchers immediately prior to a primary-care office visit. The PHQ-9 assesses how often respondents have experienced various symptoms (such as feeling down, sleep problems, thoughts of harming oneself) in the previous two weeks. Scores can range from 0 to 27. PHQ-9 results were not shared with the physicians.

For this study, the researchers focused on a specific population of 595 patients, those with a PHQ-9 score less than 10, since this group is considered to be at low risk for depression and poor candidates for taking antidepressants. In this group, most (545) did not complete a separate measure of depressive symptoms during their office visit. Very few of these patients were diagnosed with depression (10.5%), were recommended an antidepressant (1.6%), or were prescribed an antidepressant (3.8%). However, for those patients who were administered a brief depression symptom measure by their primary care provider, 20% were given a diagnosis of depression, 12% were recommended an antidepressant, and another 12% were prescribed an antidepressant.

Use of the screening measures, which was more common during office visits in HMO and Veterans Affairs settings, increased the likelihood that patients who were not likely to be depressed would receive depression treatment (odds ratio 3.2; 95% confidence interval 1.1-9.2). The study highlights the need for more research to determine the best way to use brief depression questionnaires in primary care practices, and to balance benefits and risks of treatment, including overdiagnosis of depression and the use of antidepressants (Jerant A et al, *J Am Board Fam Med* 2014;27(5);611–620).

TCPR's Take: Most psychiatrists are aware that brief symptom measures are meant to be screening tools, not diagnostic instruments. Nevertheless, this study shows that in the primary care setting these questionnaires may provide the justification for a diagnosis of depression and the prescription of antidepressants to patients who are not clinically depressed. Without more evidence to support the use of screening instruments in primary care settings, this practice should be reconsidered.

SUICIDE

Sunshine Linked to Suicide Rates

Sunshine and other forms of bright light are considered to be helpful for depressed patients. Patients with seasonal affective disorder (SAD) feel better as the days lengthen, and bright light therapy is effective for the depression in patients with and without SAD. However, seasonal studies of suicide have found that the prevalence is highest in the spring, which is counterintuitive if we consider light to be an antidepressant. A new study out of Austria clarifies this seasonal finding by separating out the effects of sunshine *per se* versus seasonality. The results are a bit perplexing.

Researchers analyzed retrospective data on all officially confirmed suicides in Austria for a 40-year period (nearly 70,000 deaths from 1970 to 2010). They then looked at data derived from meteorological stations on the average duration of sunshine per day in hours. Finally, they used mathematical techniques to separate the effect of sunshine exposure from the season.

On each day studied, independent of season, researchers found that the hours of sunshine and the number of suicides were highly correlated. They found a positive correlation between sunshine and suicide that held not only on the day of the suicide but also 10 days prior to the event. Conversely, they found a negative correlation between the number of suicides and the daily hours of sunshine for the 14 to 60 days prior to the suicide, suggesting more daily sunshine over a prolonged period may protect against suicide. This protective effect was more pronounced in men than women.

The implications are that brief exposure to sunshine may increase the risk of suicide, especially in female patients. Why this might happen is unclear. The authors hypothesize that brief sunlight might energize depressed patients before significantly improving mood, and that this could increase their motivation to do something about their condition, no matter how drastic.

Researchers said more study is needed to determine which patients with depression are most susceptible to the effects of sunshine (Vyssoki B et al, *JAMA Psychiatry* 2014; Epub ahead of print).

TCPR's Take: There were some limitations to this study—for example, it did not account for other climatic factors (such as temperature, humidity, and air pressure) that vary along with the amount of sunshine to a certain degree. While the findings may represent a statistical anomaly and need to be replicated, you might consider more closely monitoring your suicidal patients, especially women, when the weather takes a sudden turn toward sunny days.

CME Post-Test

This CME post-test is intended for participants only seeking AMA PRA Category 1 Credit™. For those seeking ABPN self-assessment (MOC) credit, a 13 question pre- and post-test must be taken online. For all others, to earn CME or CE credit, you must read the articles and log on to www.TheCarlatReport.com to take the post-test. You must answer at least four questions correctly to earn credit. You will be given two attempts to pass the test. Tests must be taken by October 31, 2015. As a subscriber to *TCPR,* you already have a username and password to log on www.TheCarlatReport.com. To obtain your username and password or if you cannot take the test online, please email info@thecarlatreport.com or call 978-499-0583.

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Below are the questions for this month's CME post-test. This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Note: Learning objectives are listed on page 1.

1. In psychiatry, pharmacogenetics studies how genetic variation influences the response of patients to which of the following (Learning Objective #1)?
   - [ ] a) Medications
   - [ ] b) Psychotherapy
   - [ ] c) Electrical brain stimulation
   - [ ] d) Biomarkers

2. According to Steven Hamilton, MD, PhD, the most appropriate time for genetic testing is before ever prescribing a medication (LO #2).
   - [ ] a) True
   - [ ] b) False

3. Suvorexant (Belsomra) works via activity at which of the following (LO #3)?
   - [ ] a) GABA receptors
   - [ ] b) Orexin receptors
   - [ ] c) Histamine receptors
   - [ ] d) Melatonin receptors

4. While sunshine and other forms of bright light are considered to be helpful for depressed patients, seasonal studies of suicide have found that the prevalence is highest in which season (LO #4)?
   - [ ] a) Winter
   - [ ] b) Spring
   - [ ] c) Summer
   - [ ] d) Fall

5. In a California study, when patients without a clear diagnosis of depression, as measured by the PHQ-9, completed a brief depression screening questionnaire with their primary care providers, what percentage were given a diagnosis of depression (LO #4)?
   - [ ] a) 5%
   - [ ] b) 15%
   - [ ] c) 20%
   - [ ] d) 35%

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Belsomra: A New Hypnotic? Don't Get Too Excited

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The Fight for FDA Approval

An interesting part of the history of this drug is that Merck expected to gain FDA approval in the summer of 2013. However, the FDA expressed concerns about safety with the 30 mg to 40 mg dosing range Merck was proposing and denied approval. The approval finally came in August with the newer, lower dosing range of 10 mg to 20 mg nightly. The next-day driving tests requested by the FDA showed that even those who took the 20 mg dose were impaired in the morning. For this reason, the recommended dose is 10 mg nightly, however, the labeling does allow for dosage increases up to 20 mg nightly. Along with the concern for next-day impairment, the usual warnings for hypnotics also apply here: avoid alcohol and other CNS depressants, exercise caution in patients who are depressed or suicidal, monitor for behavioral changes including amnesia and complex sleep behaviors (eating, texting, sex while still sleeping).

Suvorexant will be available as 5, 10, 15, and 20 mg tablets by late 2014 or early 2015. It will be a schedule IV controlled substance (same category as zolpidem (Ambien) and temazepam (Restoril), among others) although the data thus far have not shown withdrawal and rebound upon discontinuation.

TCPR'S VERDICT: Other than a new mechanism of action, there's not much to recommend suvorexant. It likely works just fine as a sleeping pill, but there's no reason to expect it to work better than the many hypnotics already on the market. We're concerned that next-day impairment is a potential side effect at the highest approved dose of 20 mg, particularly since sleepless patients may decide on their own to take even higher doses. Be very clear to patients about the potential dangers of driving the next morning. Suvorexant also will likely be expensive, and only a couple of thousand people have been exposed thus far, mostly in short-term trials. This is definitely not a first line medication—nor even a second line.

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This Month's Focus:
Pharmacogenetics

Next month in *The Carlat Psychiatry Report:* Bipolar Disorder

Pharmacogenetic Testing in Clinical Psychiatry

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in April 2014). Using the three-bin categorization scheme described previously, GeneSight ADHD classifies eight stimulant and non-stimulant drugs used for treating ADHD and GeneSight Analgesic classifies 22 opioid and non-opioid drugs. I am unaware of any published literature on clinical outcomes associated with the use of these tests.

Larger multi-center studies of genetic testing are currently underway. Cost-effectiveness will need to be assessed, as these tests are not cheap (eg, GeneSight Psychotropic is approximately $3,800) although they are sometimes covered by insurance. Forthcoming FDA guidelines will likely encourage, if not require, the assessment of clinical validity and utility of these tests before future tests go to market.

TCPR'S VERDICT: Pharmacogenetic testing is intriguing, expensive, and unlikely to be clinically useful. Until we see better evidence, buyer beware!

Correction

In the September 2014 issue of *TCPR*, we incorrectly stated in the "Q&A with the Expert" that Karl Lanocha, MD, was discussing the *off-label* use of transcranial magnetic stimulation (TMS). In fact, the US Food and Drug Administration (FDA) product labeling for the NeuroStar and Brainsway TMS devices states that these treatments are indicated for the treatment of depression in adults unresponsive to more than one antidepressant trial.